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Neurological complications following treatment of children with brain tumors

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Abstract

Brain tumors and their treatments in children result in a range of neurological complications that can affect daily function and rehabilitation potential, including neurocognitive sequelae, ototoxicity, seizure disorders, stroke, and peripheral neuropathy. Deficits in cognitive function, particularly learning and memory, attention and speed of information processing, can be debilitating. With new insights to the cellular and molecular etiology of these deficits, new therapies for cognitive decline after therapy are emerging. Management strategies for other neurological complications are also emerging.

Introduction

Structure and function are intimately linked in the nervous system. However, normal functioning of the nervous system depends upon not only the structural integrity of the brain, spinal cord and peripheral nerves, but also several dynamic physiological processes. While the majority of the nervous system forms during fetal development, many cell types continue to divide and regenerate throughout life. Astrocytic and oligodendroglial populations replenish themselves continually to maintain the integrity of the white matter, as do endothelial cells comprising the neurovasculature. These support cells are necessary for normal neuronal physiology and peripheral nerve function. Newborn neural cells, particularly the dentate granule cell neurons of the hippocampus, generate constantly throughout life. Together with ongoing maintenance of white mater tract integrity, this process of postnatal hippocampal neurogenesis is thought to be critical to proper cognitive function. These dynamic cell populations are particularly vulnerable to the cytotoxic actions of cancer therapies, particularly irradiation. Other important cell populations and neural structures are similarly susceptible to toxicity from treatments, including mature oligodendrocytes of the white matter, endothelial cells of the blood vessles, hair cells of the inner ear, and long axons of peripheral nerves. The following review will focus on neurological complications of brain tumor therapies that significantly affect quality of life and rehabilitation potential, including neurocognitive effects, seizure disorders, stroke, ototoxicity, and neuropathy.

Neural precursor cells in the childhood brain

Neural progenitor cell biology is central to the etiology of the late effects of brain tumor therapies. Neural stem cells, self-renewing cells that generate neurons, astroglia, and oligodendroglia, as well as lineage-restricted neural precursor cells, exist in the postnatal brains of all mammals studied to date, including humans [12]. Neural stem cells, neuronal

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precursor cells, and glial precursor cells are collectively known as neural progenitor cells (NPCs). Prominent populations of neural stem cells exist in the subventricular zone throughout the central nervous system [3] and in the hippocampus [2]. Lineage-restricted glial precursor cells are found throughout the subcortical white matter, and in fact, the process of postnatal myelination of the frontal lobes continues from birth through the end of the third decade of life. Maintenance of white matter tract integrity is thought to depend upon ongoing generation of glial cells (oligodendrocytes and astrocytes) from glial progenitor cells. Once thought to be a relatively static organ, the postnatal brain is now known to require ongoing cell generation from diverse progenitor cell populations in multiple germinal zones as part of normal health.

Neurocognitive Sequelae

Cognitive dysfunction, characterized by prominent dysfunction of short-term memory, is perhaps the most common sequela of brain tumor therapy. The tumor itself, neurosurgery, chemotherapy, and particularly radiotherapy can all contribute to neurocognitive sequelae. Cranial radiotherapy causes a debilitating cognitive decline in children [456]. Months to years after treatment, patients exhibit progressive deficits in memory function, spatial relations, processing speed, visual motor processing, quantitative skills and attention [78]. This pattern of cognitive impairment implies disruption of limbic and frontal networks. Hippocampal dysfunction is a prominent feature of these neuropsychological sequelae. In fact, the severity of the cognitive deterioration appears to depend upon the radiation dosage delivered to the medial temporal lobes [9].

The incidence of treatment–induced impairment in cognition has been very well described in children. It is estimated that, when irradiated at age less than 7 year, nearly 100% of children require special education; after 7 years of age approximately 50% of children require special education[10]. Very young children (age < three years) are exquisitely vulnerable to radiation [11]. Some degree of memory dysfunction is thought to occur in the majority of children, including a progressive decline in intelligence quotient (IQ) [12]. The use of stimulants such as methylphenidate can help to mitigate some cognitive symptoms, such as poor attention and daytime fatigue [1314]. While some have proposed use of modafinil or intensive cognitive rehabilitation to mitigate symptoms, these strategies are still under investigation. Insights to the etiology of cognitive dysfunction following therapy for brain tumors will hopefully lead to neuroprotective strategies in the future.

Cellular etiology of neurocognitive sequelae

Radiation

The cognitive dysfunction that follows radiotherapy is inconsistently associated with radiological findings, and frequently occurs in patients with normal-appearing neuroimaging [15]. A clinically significant memory deficit in the absence of radiological findings implicates damage to a subtle process with robust physiological consequences.

One such neurophysiological process is hippocampal neurogenesis. Studies in animal models have demonstrated that therapeutic doses of cranial irradiation virtually ablate neurogenesis [161718], and that this inhibition of neurogenesis correlates with impaired performance on hippocampal-dependent memory tests [19]. Surprisingly, irradiation does not simply deplete the stem cell population, but rather disrupts the microenvironment that normally supports hippocampal neurogenesis [17]. This microenvironmental perturbation is due largely to irradiation-induced microglial inflammation, and anti-inflammatory therapy with the nonsteroidal anti-inflammatory agent indomethacin partially restores hippocampal neurogenesis and function in rodents [20]. Studies of human postmortem samples have also

confirmed ablation of hippocampal neurogenesis following cranial radiotherapy in childhood [21] Clinical trials are currently underway to evaluate the clinical safety and utility of anti-inflammatory therapy to limit hippocampal inflammation during cranial radiotherapy. Additional strategies to restore neurogenesis following radiation therapy are emerging from the preclinical literature (Table 1). Blocking the deleterious effects of inflammation on mitochondria using mitochondrial protectants, such as the vitamin thiamine, during radiation exposure improves neuroblast survival and results in a two-fold increase in neurogenesis [22]. Aerobic exercise, a potent pro-neurogenic activity due to peripheral VEGF elaboration [23] improves hippocampal neurogenesis even after radiation exposure [24]. Whether other interventions, such as antioxidants, preclude or help minimize radiation-induced injury remains an experimental question.

Additional factors that may contribute to cognitive dysfunction following cranial radiation therapy include subtle white matter dysfunction and altered regional blood flow due to microvascular disease [258].

Chemotherapy

Many chemotherapeutic agents have now been demonstrated to have toxic effects on multiple neural cell types, affecting both proliferating and static cells of the central nervous system. For example, methotrexate, an anti-metabolite with a particularly high incidence of neurotoxic effects, induces cell death in multiple neural cell types, including neurons, in both *in vitro* and *in vivo* model systems [26]. Particularly vulnerable to methotrexate toxicity are the glial progenitor cells that form myelinating oligodendrocytes and astrocytes, both critical to white matter integrity [27]. Further studies have confirmed and delineated the particular chemo-sensitivity of neural precursor cells, including both neural stem as well as lineage-restricted progenitor cells that form, among other cell types, the myelinating oligodendrocytes in the frontal white matter [28]. A wide range of agents, including BCNU, cisplatin, and cytarabine have proved to be more toxic to neural precursor cells than cancer cells.[28]. In addition to their precursor cells, mature myelinating oligodendrocytes are exquisitely sensitive to chemotherapeutic agents at dosages lower than those required to kill most tumor cells [2829]. Following single drug exposures in an *in vivo* animal model, rebound cell proliferation in germinal zones implies that compensatory mechanisms may replace the lost cells; disturbingly, repetitive drug exposures (BCNU, cisplatin, or cytarabine) ablate this proliferative response, suggesting a depletion of the precursor pool [28]. Consistent with this finding, toxicity to oligodendrocyte progenitors and myelinating oligodendrocytes causes progressive damage to white matter in a rodent model after short-term 5-fluorouracil exposure at clinically-relevant doses [29].

Multiple chemotherapeutic agents similarly affect the precursor cells that contribute to hippocampal neurogenesis. Like radiation exposure, systemic methotrexate administration causes a persistent decrease in cell proliferation within the germinal region of the hippocampus and associated poor performance on hippocampal-dependent cognitive tasks in rodent models [3031].

Seizures

Seizures are a frequent in children with brain tumors, both at the time of presentation and as a long-term consequence [32]. Seizure disorders can arise from epileptic foci that result from the original tumor or from sequelae of surgery, radiation, or chemotherapy, such as gliosis or stroke. Supratentorial tumors are more frequently associated with seizures than those occurring in the posterior fossa [32]. The prevalence of seizures among 5-year survivors is approximately 30% compared to siblings, and in the remainder who have not had a seizure by 5 years after tumor diagnosis, there is still a 15-fold risk of new–onset seizures, compared

to controls.[33] Risk factors for seizure disorders following brain tumor therapy include radiation of greater than 30Gy involving any cortical area [34]. Once manifest, seizure disorders are managed with antiepileptic drugs as for any patient, although among survivors of brain tumors there is often attention to use drugs with less potential for cognitive impairment, hepatoxicity, or drug interactions. Prophylactic use of anti-epileptic drugs is not indicated in patients without a history of seizures. Levetiracetam and lamotrigine are increasingly being used when necessary in this population.

Stroke

Cranial irradiation for a brain tumor is associated with latent cerbrovascular disease, with some patients carrying a particularly increased risk [35]. The most common underlying vascular disturbances that lead to stroke in survivors of childhood brain tumors are venous-based cavernous malformations, small vessel telangectasias, aneurysms, moyamoya disease, and mineralizing microangiopathy. In all these pathologies there tends to be underlying injury to endothelial cells of the blood vessel wall. The cumulative incidence of stroke, typically ischemic rather than hemorrhagic, 25 years after treatment in children has been reported by one study as high as 6.9%. [36]. Factors which increase risk are radiation dose >30 Gy, particularly to the middle cranial fossa; neurofibromatosis; obesity; insulin resistance; and suboptimal fitness level. Thus, among brain tumor survivors, attention should be focused as years pass to identifying and modifying risk factors (e.g., elevated hemoglobin A1C, hypertension, high cholesterol, inactivity) that presdipose to stroke. Asymptomatic vascular pathology may be noted on routine follow-up brain MRIs to detect tumor, but intervention is rarely warranted. Some children who develop moyamoya disease may be candidates for vascular shunting procedures.

Ototoxicity

Posterior and middle cranial fossa radiotherapy and platinum-based chemotherapy both contribute to sensorineural ototoxicity and hearing loss. Toxicity to cochlear hair cells is central to the etiology of treatment-related hearing loss and results in deficits hearing sounds in the high frequency range. The damage is typically irreversible and bilateral, although may not always be symmetrical [37]. In a large cohort study of 5 year survivors of various pediatric brain tumors, the prevalence of self-reported hearing loss or deafness was 20% compared to siblings [33]. Prevalence is even higher in patients treated for tumors requiring > 50Gy radiation to the posterior fossa and cisplatin chemotherapy [34]. Hearing loss in the higher frequencies of sound ranges affects approximately 50 – 70% of children receiving cisplatin [383940]. Severity of hearing loss depends upon the cumulative dose of cisplatin, and may progressively worsen over the course of the first two years after therapy [41]. In comparison to cisplatin, carboplatin use alone is rarely ototoxic [4140]; however combined use of cisplatin and carboplatin appears to be synergistic with regard to hearing loss [40]. Hearing loss is a relatively common sequela of brain tumor therapy that can affect speech and language development and academic performance, especially in younger children. Close monitoring with audiological testing and intervention with hearing aids as appropriate can help to mitigate the impact of the hearing loss. Current radiation therapy practices employing conformal techniques has reduced radation-induced damage of the cochlea, but use of amifostine or N-acetylaspartate to prevent cisplatin damage to hair cells has not yet proved to be an effective strategy.

Neuropathy

Vinca alkaloids, most prominently vincristine and to a lesser extent vinblastine and vinorelbine, are commonly used to treat brain tumors and frequently cause peripheral neuropathy. Through disruption of axonal microtubules, vincristine causes an axonal

neuropathy affecting both sensory and motor fibers in almost all patients. Small sensory fibers are particularly affected. Clinical manifestations include finger tip and foot parasthesias, muscle cramps, foot and wrist drop and sensory loss of varying degrees. Focal neuropathies and cranial neuropathies are also possible. In addition the sensory and motor neuropathy, vincristine commonly causes an autonomic neuropathy, characterized by gastrointestinal, urinary and/or sexual dysfunction. Neuropathy after vinca alkaloid use can be particularly severe in patients with an underlying inherited neuropathy, such as Charcot-Marie-Tooth disease [42] and care must be taken to avoid their use in such patients. In pediatric patients, for whom genetic neuropathies are frequently not yet manifest, a careful family history can elicit the possible predisposition to severe neuropathy with use of agents like vincristine. Following therapy, the neuropathy typically improves with time, although patients, especially children treated at an older age, may not recover completely and a mild foot drop is often evident even many years after the completion of therapy. Long-term use of ankle-foot orthoses or other habilitative devices may be required for select patients.

Other Complications

Children may experience a number of other chronic neurological conditions from brain tumors and respective treatments, such as pain, migraine, balance difficulties, weakness or hemiparesis, tremor or other movement disorders, or visual loss. These problems are best addressed as they arise, by a multi-disciplinary team including a physical medicine and rehabilitation doctor, neurologist, neurosurgeon, ophthalmologist, and/or pain specialist. For additional management recommendations, the reader is referred to the Children's Oncology Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (www.survivorshipguidelines.org)

Conclusions

Common neurological sequelae of brain tumor therapy, including cognitive impairment, ototoxicity, seizure disorders and neuropathy pose significant hurdles to everyday life and to the rehabilitation process. Damage to vulnerable cell populations and structures is central to the neurological complications of brain tumor therapy. Increased understanding of the underlying mechanisms for these neurologic complications, and methods to prevent them, will be an important challenge for the future and will hopefully lead to reduced neurological morbidity in pediatric brain tumor patients.

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Table 1

Potential interventions to improve hippocampal neurogenesis after radiation

• Non-steroidal anti-inflammatory drugs (indomethacin) [16]
• Mitochondrial protectants (thiamine) [22]
• Aerobic exercise [24]